DIAGNOSTIC ACCURACY OF CORRECTED QT INTERVAL AS SURROGATE MARKER IN DIABETES MELLITUS PATIENTS WITH CARDAC AUTONOMIC NEUROPATHY

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GENERAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation titled **"DIAGNOSTIC ACCURACY OF CORRECTED QT INTERVAL AS SURROGATE MARKER IN DIABETES MELLITUS PATIENTS WITH CARDAC AUTONOMIC NEUROPATHY"** is the bonafide original work of **Dr. G. KOTHAI** in partial fulfillment of the regulation for M.D. Branch–I (General Medicine) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in April 2012. The Period of study was from May 2010 to August 2011.

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I, **Dr. G. KOTHAI**, solemnly declare that dissertation titled "**DIAGNOSTIC ACCURACY OF CORRECTED QT INTERVAL AS SURROGATE MARKER IN DIABETES MELLITUS PATIENTS WITH CARDAC AUTONOMIC NEUROPATHY"** is a bonafide work done by me at K.A.P.V. Govt. Medical College from May 2010 to August 2011 under the guidance and supervision of my unit chief **Prof. ASHOK KUMAR, M.D.,** Professor of medicine.

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ABSTRACT

Objectives

To study the prevalence and risk factors for cardiac autonomic neuropathy (CAN) and the utility of prolongation of corrected QT interval (QTc) in the ECG to diagnose CAN in patients with diabetes mellitus.

Design and setting

Cross-sectional study conducted among 100 patients attending the diabetic clinic of K.A.P.V. Govt. Medical College, Trichy.

Methods

The prevalence of CAN among 100 patients with type 2 diabetes mellitus was assessed by the five autonomic function tests by Ewing's methodology. The CAN score in each patient and its relationship to the QTc interval were analysed. Possible influences of duration of diabetes and heart rate variability on the occurrence of CAN also were studied.

Results

The prevalence of CAN was 58 %.Significant risks for CAN among patients with type 2 diabetes were prolonged QTc , reduced heart rate variability and disease duration over 10 years . Disease duration over 10 years resulted in QTc prolongation in a significant numbers of cases with type 2 diabetes. The sensitivity, specificity and positive predictive value of QTc

prolongation for the diagnosis of CAN were77%, 81% and 93.85% respectively. Higher CAN scores correlated with longer QTc intervals ($p<0.001$).

Conclusions

The prevalence of CAN in diabetes mellitus is high. Longer duration of diabetes is a significant risk factor. QTc interval in the ECG can be used to diagnose CAN with reasonable sensitivity, specificity and positive predictive value.

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ABBREVIATIONS

ACE	-	Angiotensin Converting Enzyme
ANS	-	Autonomic Nervous System
BP	-	Blood Pressure
CAN	-	Cardiovascular Autonomic Neuropathy
CI	-	Confidence Interval
DAN	-	Diabetic Autonomic Neuropathy
ECG	-	Electro Cardio Gram
E:I Ratio	-	Expiration-to-Inspiration Ratio
HDL	-	High Density Lipoprotein
HRV	-	Heart Rate Variability
LDL	-	Low Density Lipoprotein
LV	-	Left Ventricle
LVDD	-	Left Ventricular Diastolic Dysfunction
MI	-	Myocardial Infarction
MIBG	-	Metaiodo Benzyl Guanidine
OH	-	Orthostatic Hypertension

CONTENTS

INTRODUCTION

INTRODUCTION

Patients with diabetes mellitus are at an increased risk of dying from cardiovascular diseases, the reason for which is not completely understood. Excess cardiovascular risk in this population persists even after normalisation for other conventional cardiovascular risk factors (hypertension, dyslipidaemia, physical inactivity, smoking) suggesting that there are other incompletely understood mechanisms which increase cardiovascular risk in diabetic patients. Ventricular instability, as manifested in QT abnormalities, might be an important additional mechanism.

The electrocardiographic QT interval has been extensively studied in ischaemic heart disease. Recently, there has been increasing interest in the relationship between diabetes and QT abnormalities. QT prolongation and increased QTd have been shown to predict cardiac death in both type 1 and type 2 diabetes mellitus. Although there is general agreement that QT interval is affected by cardiac ischaemia, the effect of hyperglycaemia on QT measures is controversial. First, there is controversy as to whether the measure has any physiological meaning; secondly, there is no universally accepted method of measurement and hence no consensus about the upper limit of normal.

Nevertheless, several studies have shown increased QT in diabetic patients suggesting that assessment of the QT interval could be a cost effective way of stratifying such patients according to cardiovascular risk so that aggressive treatment could be directed appropriately to improve outcome.

In 1980, for the first time, an association of prolonged QTc interval with cardiac autonomic neuropathy was given, thereby opening the possibility of a rapid objective method for detecting cardiac autonomic neuropathy. Further studies demonstrated an association of prolonged QTc interval with cardiac dysautonomia in diabetes mellitus.

This study is performed to estimate the Prevalence of Cardiovascular Autonomic Neuropathy with relation to duration of diabetes in our GH and to check the accuracy of corrected QT interval in diagnosing it.

AIMS AND OBJECTIVES

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1. To evaluate the prevalence of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes patients in our hospital.
2. To correlate the prevalence of Cardiovascular Autonomic Neuropathy with duration of diabetes.
3. To evaluate the relationship between Cardiac Autonomic Neuropathy and QTc interval prolongation.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The autonomic nervous system modulates the electrical and contractile activity of the myocardium via the interplay of sympathetic and parasympathetic activity. An imbalance of autonomic control is implicated in the pathophysiology of arrhythmogenesis. Cardiovascular autonomic neuropathy (CAN), a common form of autonomic dysfunction found in patients with diabetes mellitus, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics. Individuals with parasympathetic dysfunction have a high resting heart rate most likely because of vagal neuropathy that results in unopposed increased sympathetic outflow. Persons with a combined parasympathetic /sympathetic dysfunction have slower heart rates. With advanced nerve dysfunction, heart rate is fixed. Thus, it is apparent that the determination of heart rate itself is not a reliable diagnostic sign of CAN. Reduction in variability of heart rate is the earliest indicator of CAN. Clinical manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension (OH), asymptomatic ischemia, painless myocardial infarction (MI), and increased risk of mortality. A recent publication by the American Diabetes Association highlighted the significance of diabetic neuropathy by issuing a statement for healthcare professionals that provides guidelines for prevention, detection, and management of neuropathy.

Cardiovascular autonomic neuropathy (CAN) is a common form of autonomic neuropathy, causing abnormalities in heart rate control and central and peripheral vascular dynamics. Cardiovascular autonomic neuropathy has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction. Cardiovascular autonomic neuropathy occurs in ~17% of patients with type 1 diabetes and 22% of those with type 2. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction.

Cardiac Autonomic Neuropathy

Perhaps one of the most overlooked of all serious complications of diabetes is CAN[1]. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics[2]. Reduced heart rate variation is the earliest indicator of CAN[3].

In a review of several epidemiological studies among individuals have demonstrated that the 5-year mortality rate is five times higher for individuals with CAN than for individuals without cardiovascular autonomic involvement[4].

Clinical manifestations of Cardiac Autonomic Neuropathy

Exercise intolerance

Autonomic dysfunction can impair exercise tolerance[5]. Kahn et al.[6] have shown a reduced response in heart rate and blood pressure during exercise

in individuals with CAN. In the study done by Roy et al.[7] there was a decrease in cardiac output in response to exercise in individuals with CAN. The severity of CAN has also been shown to correlate inversely with an increase in heart rate at any time during exercise and with the maximal increase in heart rate. It is also noted that decreased ejection fraction, systolic dysfunction, and diastolic filling will limit exercise tolerance[8]. Given the potential for impaired exercise tolerance, it has been suggested that diabetic patients who are likely to have CAN have cardiac stress testing before undertaking an exercise program[9].

Intraoperative cardiovascular liability

Hemodynamic changes occur during surgery for individuals with and without diabetes. A study done by Burgos et al.[10] showed that vasopressor support was needed more often in diabetic individuals with autonomic dysfunction than in those without. The normal autonomic response of vasoconstriction and tachycardia did not completely compensate for the vasodilating effects of anesthesia. A study done by Kitamura et al.[11] also recently demonstrated an association between CAN and more severe intraoperative hypothermia. Complications arising from intraoperative hypothermia include decreased drug metabolism and impaired wound healing. Sobotka et al.[12] in his study showed that some diabetic patients with autonomic neuropathy have a reduced hypoxic-induced ventilatory drive. These data suggest that preoperative cardiovascular autonomic screening may provide useful information for anesthesiologists planning the anesthetic management of diabetic patients and identify those at greater risk for intraoperative complications.

Orthostatic hypotension

In patients with diabetes, orthostatic hypotension is usually due to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature[14]. In addition, there is a decrease in cutaneous, splanchnic and total vascular resistance that occurs in the pathogenesis of this disorder.

Normally, in response to postural change there is an increase in plasma norepinephrine. For individuals with orthostatic hypotension, there may be a reduction in this response relative to the fall in blood pressure[15]. Diminished cardiac acceleration and cardiac output, particularly in association with exercise, may also be an important mechanism. Less frequently, there is a rise in norepinephrine that may be due to low blood volume or reduced red cell mass. Frequently, there are fluctuations in the degree of orthostatic hypotension. This may reflect postprandial blood pooling, the hypotensive role of insulin, and changing patterns of fluid retention due to renal failure or congestive heart failure.

Patients with orthostatic hypotension typically present with lightheadedness and presyncopal symptoms. Symptoms such as dizziness, weakness, fatigue, visual blurring, and neck pain also may be due to orthostatic hypotension. Many patients, however, remain asymptomatic despite significant falls in blood pressure. If the cause of orthostatic hypotension is CAN, treatment goals should not only consist of therapies to increase the standing

blood pressure, balanced against preventing hypertension in the supine position, but should also provide education to patients so that they avoid situations (e.g., vasodilation from hot showers) that result in the creation of symptoms (i.e., syncopal episodes). Such symptoms can result in injuries from falling. Cardiovascular autonomic function testing may help differentiate CAN from other causes of weakness, lightheadedness, dizziness, or fatigue and promote appropriate therapeutic intervention.

Silent myocardial ischemia / cardiac denervation syndrome

The cause of silent myocardial ischemia in diabetic patients is controversial. It is clear, however, that a reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction and thereby delay appropriate therapy.

12 cross-sectional studies, comparing the presence of silent myocardial ischemia, generally measured by exercise stress testing between diabetic individuals with and without CAN were analysed. Of the 12 studies, 5 showed a statistically significant increased frequency of silent myocardial ischemia in individuals with CAN compared with individuals without CAN. Via meta-analysis, the Mantel-Haenszel estimate for the pooled prevalence rate risk for silent myocardial ischemia was 1.96, with a 95% CI of 1.53–2.51 ($P < 0.001$; n = 1,468 total subjects). These data demonstrate a consistent association between CAN and the presence of silent myocardial ischemia.

A study done by Ambepityia et al.[16] measured the anginal perceptual threshold (i.e., the time from onset of 0.1 mV ST depression to the onset of angina pectoris during exercise) in individuals with and without diabetes. The perception of angina was severely impaired in the diabetic patients, allowing these individuals to exercise longer after the onset of myocardial ischemia. The delay in perception of angina was associated with the presence of cardiovascular autonomic dysfunction. The investigators suggested that the neuropathic damage to the myocardial sensory afferent fibers in the autonomic nerve supply reduced the diabetic individual's sensitivity to regional ischemia by interrupting pain transmission. Marchant et al.[17] examined 22 diabetic and 30 nondiabetic individuals who had similar left ventricular function and severity of coronary artery disease as assessed by coronary angiography and ventriculography. The following autonomic function tests were included: heart rate variation during deep breathing (beats/min), 30:15 ratio, Valsalva maneuver, blood pressure response to standing, and blood pressure response to sustained handgrip. All 52 individuals manifested ischemia during exercise. A total of 16 individuals did not experience angina, and 10 of these had diabetes. Comparing the silent ischemia group (n = 16) with the group who did experience angina (n = 36) revealed impaired autonomic function in the silent ischemia group, with statistically lower 30:15 ratios. Hikita et al.[18], used 24-h ambulatory ECG recordings and demonstrated that HRV is reduced in diabetic

patients with silent ischemia when compared with nondiabetic individuals with silent or painful ischemia.

The presence of CAN does not exclude painful myocardial infarction (MI) among individuals with diabetes[19]. Chest pain in any location in a patient with diabetes should be considered to be of myocardial origin until proven otherwise; but, of equal importance, unexplained fatigue, confusion, tiredness, edema, hemoptysis, nausea and vomiting, diaphoresis, arrhythmias, cough, or dyspnea should alert the clinician to the possibility of silent MI.

Increased risk of mortality

In a study done by Ewing et al.[20] the 2.5-year mortality rate of 27.5% increased to 53% after 5 years in diabetic patients with abnormal autonomic function tests compared with a mortality rate of only 15% over the 5-year period among diabetic patients with normal autonomic function test results. It is also noted that half of the deaths in individuals with abnormal autonomic function tests were from renal failure, and 29% were from sudden death. This study also revealed that symptoms of autonomic neuropathy, especially postural hypotension, and gastric symptoms in the presence of abnormal autonomic function tests carried a particularly poor prognosis.

A study by O'Brien[21] reported 5-year mortality rates of 27% in patients having asymptomatic autonomic neuropathy compared with an 8% mortality rate in diabetic subjects with normal autonomic function tests.

Rathmann et al.[22] designed a study to assess the risk of mortality due to CAN among patients with CAN but without a clinical manifestation of severe complications (proteinuria, proliferative retinopathy, coronary artery disease, or stroke) 8 years after their first clinical examination. The mortality of diabetic patients with CAN increased steadily over the 8-year period (6% after 2 years, 14% after 4 years, 17% after 6 years, and 23% after 8 years) compared with an age-, sex-, and duration of diabetes-matched control group where there was one death. Autonomic dysfunction was found to be an independent risk factor with poor prognosis. Some autonomic neuropathic symptoms (orthostatic hypotension, gastroparesis, gustatory sweating and erectile impotence) were found more frequently among subjects who died.

A population-based study (the Hoorn study) examined 159 individuals with type 2 diabetes (85 had newly diagnosed diabetes) who were followed for an average of nearly 8 years. All-cause as well as cardiovascular mortality were found to be associated with impaired autonomic function in this study. The investigators also suggested that cardiovascular autonomic dysfunction in individuals already at high risk (e.g., those with diabetes, high blood pressure, or a history of cardiovascular disease) may be particularly hazardous[24].

Potential reasons for the increased mortality rate associated with CAN

Despite the increased association with mortality, the causative relationship between CAN and the increased risk of mortality has not been conclusively established. Several mechanisms have been suggested including a

relationship with autonomic control of respiratory function. Page and Watkins[26] reported 12 cardiorespiratory arrests in eight diabetic individuals with severe autonomic neuropathy and suggested that diabetic individuals with CAN have impaired respiratory responses to conditions of hypoxia and may be particularly susceptible to medications that depress the respiration system. An impaired ability to recognize hypoglycemia and impaired recovery from hypoglycemic episodes due to defective endocrine counterregulatory mechanisms are also potential reasons for death. Clarke et al.[27] speculated that the increased mortality found for patients with clinical symptoms of autonomic neuropathy were due to both a direct effect of the autonomic neuropathy itself and an indirect, but parallel, association with accelerating microvascular complications. A study conducted by O'Brien et al. suggested that the high rate of mortality due to end-stage renal disease among diabetic patients with autonomic neuropathy may have been due to the parallel development of late-stage neuropathy and nephropathy. The presence of autonomic neuropathy may accelerate the rate of progression of diabetic glomerulopathy by mechanisms not completely understood. A consequential increase in cardiovascular risk experienced by individuals with nephropathy has also been noted. In one study of type 1 diabetic individuals, hypertension along with LDL and HDL cholesterol concentrations were found to be independent correlates of CAN[28]. These results suggested that a disturbed cardiovascular risk profile seen in individuals with nephropathy might lead to both cardiovascular disease and

CAN. Other investigators have also shown independent associations of autonomic dysfunction with markers of cardiovascular risk (e.g., elevated blood pressure[29], body weight, glycosylated hemoglobin, and overt albuminuria[30]). Long-term follow-up studies are needed to distinguish the exact roles of cardiovascular risk factors, nephropathy, and CAN in the etiology of cardiovascular disease. Nonetheless, CAN cosegregates with indexes of macrovascular risk, which may contribute to the marked increase in cardiovascular mortality. Diabetic patients with CAN are predisposed to a lack of the normal nighttime decrease in blood pressure because of an increased prevalence of sympathetic activity[31]. A disturbed circadian pattern of sympathovagal activity with prevalent nocturnal sympathetic activity combined with higher blood pressure values during the night and increased left ventricular hypertrophy could represent another important link between CAN and an increased risk of mortality.

CAN and sudden death

A number of researchers have reported sudden unexpected deaths among subjects identified with autonomic neuropathy. One potential cause of sudden death may be explained by severe but asymptomatic ischemia, eventually inducing lethal arrhythmias[32]. An autonomic imbalance resulting in QT prolongation may predispose individuals to life-threatening cardiac arrhythmias and sudden death[33]. Results from the EURODIAB IDDM Complications Study showed that male patients with impaired HRV had a

higher corrected QT prolongation than males without this complication[34]. Imaging of myocardial sympathetic innervation with various radiotracers (e.g., meta-iodobenzylguanidine) has shown that predisposition to arrhythmias and an association with mortality may also be related to intracardiac sympathetic imbalance[35].

Heart failure is common in individuals with diabetes, identified by the presence of neuropathy, even in individuals without evidence of coronary artery disease or left ventricular dysfunction[36].

Increased mortality after an MI

Mortality rates after an MI are also higher for diabetic patients than for nondiabetic patients. This may be due to autonomic insufficiency, increasing the tendency for development of ventricular arrhythmia and cardiovascular events after infarction. Fava et al.[37] in his study showed that the presence of autonomic neuropathy contributed to a poor outcome in a study of 196 post-MI diabetic patients. Katz et al. showed that a simple bedside test that measured 1-min HRV during deep breathing was a good predictor of all-cause mortality for 185 patients (17.8% with diabetes) after a first MI.

Dysfunction of the ANS is associated with increased risk of mortality in individuals with diabetes. Though the exact pathogenic mechanism is unclear, it is realized that some deaths may be avoidable through early identification of these higher-risk patients and by slowing, with therapy, the progression of autonomic dysfunction and its associated conditions.

Association of cerebrovascular disease and CAN

The frequency of ischemic cerebrovascular events is increased in individuals with type 2 diabetes. Toyry et al. examined the impact of autonomic dysfunction on the risk of the development of strokes. He followed a group of 133 type 2 diabetic patients for 10 years. During the study period, 19 individuals had one or more strokes. Abnormalities of parasympathetic and sympathetic autonomic function were found to be independent predictors of stroke in this cohort.

Progression of CAN

Results of the cardiovascular autonomic function tests that are mediated mainly by the parasympathetic nervous system (e.g., heart rate response to deep breathing) are typically abnormal before those responses that are mediated by the sympathetic nerves. Although one might speculate then that parasympathetic damage occurs before sympathetic damage, this may not always be true. The increased frequency of abnormalities detected via tests of the parasympathetic system may merely be a reflection of the test (e.g., sensitivity) and not of the natural history of nerve fiber damage. Thus, it may be better to describe the natural history of autonomic dysfunction as developing from early to more severe involvement rather than to anticipate a sequence of parasympathetic to sympathetic damage.

Although much remains to be learned about the natural history of CAN, previous reports can be coalesced into a few observations that provide some insight with regard to progression of autonomic dysfunction:

- It can be detected at the time of diagnosis.
- Neither age nor type of diabetes are limiting factors in its emergence, being found in young individuals with newly diagnosed type 1 diabetes and older individuals newly diagnosed with type 2 diabetes.
- Poor glycemic control plays a central role in development and progression.
- Intensive therapy can slow the progression and delay the appearance of abnormal autonomic function tests.
- Subclinical autonomic neuropathy can be detected early using autonomic function test.
- Autonomic features that are associated with sympathetic nervous system dysfunction (e.g., orthostatic hypotension) are relatively late complications of diabetes.
- There is an association between CAN and diabetic nephropathy that contributes to high mortality rates.

CLINICAL TESTING OF AUTONOMIC FUNCTION

Assessing cardiovascular autonomic function

Quantitative tests of autonomic function have historically lagged behind measures of motor nerve function and sensory nerve function deficits. The lack of interest in the development of such measures was partly due to the erroneous but commonly held view that autonomic neuropathy was only a small and relatively obscure contributor to the peripheral neuropathies affecting individuals with diabetes.

In the early 1970s, Ewing et al.[38] proposed five simple noninvasive cardiovascular reflex tests (i.e., Valsalva maneuver, heart rate response to deep breathing, heart rate response to standing up, blood pressure response to standing up, and blood pressure response to sustained handgrip) that have been applied successfully by many. The clinical literature has consistently identified these five tests as they have been widely used in a variety of studies. The tests are valid as specific markers of autonomic neuropathy if end-organ failure has been carefully ruled out and other potential factors such as concomitant illness, drug use (including antidepressants, over-the-counter antihistamines and cough/cold preparations, diuretics, and aspirin), lifestyle issues (such as exercise, smoking, and caffeine intake), and age are taken into account. A large body of evidence indicates that these factors can, to various degrees, affect the cardiovascular ANS and potentially other autonomic organ systems.

Heart rate response to deep breathing is for the most part a function of parasympathetic activity, although the sympathetic nervous system may affect this measure. Similarly, it is parasympathetic activity that plays the greatest role in the heart rate regulation for short-term standing, where the act of standing involves low-level exercise and parasympathetic tone is withdrawn to produce a sudden tachycardic response. In response to subsequent underlying blood pressure changes while standing, a baroreceptor-mediated reflex involves the sympathetic nerves for further heart rate control. Heart rate response to the Valsalva maneuver is influenced by both parasympathetic and sympathetic

activity. Measurements of blood pressure response to standing and blood pressure response to sustained handgrip are used to assess sympathetic activity.

Heart rate response to deep breathing (i.e., beat-to-beat heart rate variation, R-R variation)

Beat-to-beat variation in heart rate with respiration depends on parasympathetic innervation. Pharmacological blockade of the vagus nerve with atropine all but abolishes respiratory sinus arrhythmia, whereas sympathetic blockade with the use or pretreatment of propranolol has only a slight effect on it. Several different techniques have been described in clinical literature, but measurement during paced deep breathing is considered the most reliable. The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while a heart monitor records the difference between the maximum and minimum heart rates. Over a number of years, there have been several different measures of R-R variation. The following six measures have most consistently been reported (standard deviation, coefficient of variation, mean circular resultant, maximum minus minimum, expiration-to-inspiration [E:I] ratio, and spectral analysis). There are advantages, disadvantages, and considerations that need to be recognized for all of the measures of R-R variation.

Heart rate response to standing

This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. The typical heart rate response to standing is

largely attenuated by a parasympathetic blockade achieved with atropine. In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30th beat after standing. In patients with diabetes and autonomic neuropathy, there is only a gradual increase in heart rate. The patient is connected to an electrocardiogram (ECG) monitor while lying down and then stands to a full upright position. ECG tracings are used to determine the 30:15 ratio, calculated as the ratio of the longest R-R interval (found at about beat 30) to the shortest R-R interval (found at about beat 15). Because the maximum and minimum R-R intervals may not always occur at exactly the 15th or 30th beats after standing, Ziegler et al.[39] redefined the maximum / minimum 30:15 ratio as the longest R-R interval during beats 20–40 divided by the shortest R-R interval during beats 5–25.

Valsalva maneuver

The reflex response in healthy subjects to the Valsalva maneuver includes tachycardia and peripheral vasoconstriction during strain, followed by an overshoot in blood pressure and bradycardia after release of strain. The response is mediated through alternating activation of parasympathetic and sympathetic nerve fibers. Pharmacological blockade studies using atropine, phentolamine (an α-adrenergic antagonist), and propranolol (a nonspecific β-adrenergic blocker) confirm dual involvement of autonomic nerve branches

for the response to this maneuver by demonstrating the drugs' varied effects of attenuation or augmentation of the hemodynamic response to the maneuver at specific times during the response .In patients with autonomic damage from diabetes, the reflex pathways are damaged. This is seen as a blunted heart rate response and sometimes as a lower-than-normal decline in blood pressure during strain, followed by a slow recovery after release.

In the standard Valsalva maneuver, the supine patient, connected to an ECG monitor, forcibly exhales for 15 s against a fixed resistance (40 mmHg) with an open glottis. A sudden transient increase in intrathoracic and intra-abdominal pressures, with a consequent hemodynamic response, results.

The response to performance of the Valsalva maneuver has four phases and in healthy individuals can be observed as follows:

- **Phase I:** Transient rise in blood pressure and a fall in heart rate due to compression of the aorta and propulsion of blood into the peripheral circulation. Hemodynamic changes are mostly secondary to mechanical factors.
- **Phase II:** Early fall in blood pressure with a subsequent recovery of blood pressure later in the phase. The blood pressure changes are accompanied by an increase in heart rate. There is a fall in cardiac output due to impaired venous return causing compensatory cardiac acceleration, increased muscle sympathetic activity, and peripheral resistance.

- **Phase III:** Blood pressure falls and heart rate increases with cessation of expiration.
- **Phase IV:** Blood pressure increases above the baseline value (overshoot) because of residual vasoconstriction and restored normal venous return and cardiac output.

The Valsalva ratio is determined from the ECG tracings by calculating the ratio of the longest R-R interval after the maneuver (reflecting the bradycardic response to blood pressure overshoot) to the shortest R-R interval during or shortly after the maneuver (reflecting tachycardia as a result of strain).

Levitt et al.[40] showed that the rate of deterioration of the Valsalva ratio was 0.015 per year for individuals with type 1 diabetes, which was more than twice that expected from cross-sectional studies of the aging effect in normal individuals of a similar age range.

Assessing cardiovascular adrenergic (sympathetic) function

Systolic blood pressure response to standing

Blood pressure normally changes only slightly on standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex-mediated peripheral vasoconstriction and tachycardia. In normal individuals, the systolic blood pressure falls by < 10 mmHg in 30 s.

In diabetic patients with autonomic neuropathy, baroreflex compensation is impaired. A response is considered abnormal when the diastolic blood pressure decreases more than 10 mmHg or the systolic blood pressure falls by 30 mmHg within 2 min after standing. A task force of the American Academy of Neurology (AAN) and the American Autonomic Society defined orthostatic hypotension as a fall in systolic blood pressure of ≥ 20 mmHg or diastolic blood pressure of ≥ 10 mmHg accompanied by symptoms[41].

Diastolic blood pressure response to sustained handgrip

In this test, sustained muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. This rise is caused by a reflex arc from the exercising muscle to central command and back along efferent fibers. The efferent fibers innervate the heart and muscle, resulting in increased cardiac output, blood pressure, and heart rate. The dynamometer is first squeezed to isometric maximum, then held at 30% maximum for 5 min. The normal response is a rise of diastolic blood pressure >16 mmHg, whereas a response of <10 mmHg is considered abnormal. Patients with DAN are more likely to exhibit only a small diastolic blood pressure rise.

Response to tilting

The hemodynamic response to standing is a commonly performed measure of autonomic function. Passive head-up tilting provides a more precise

level of standardization to the orthostatic stimulus and reduces the muscular contraction of the legs, which can reduce lower-leg pooling of blood. A tilt angle of 60° is commonly used for this test. The tilt may be maintained for 10–60 min or until the patient's orthostatic symptoms can be reproduced. The orthostatic stress of tilting evokes a sequence of compensatory cardiovascular responses to maintain homeostasis. As for the stand response, the normal tilted reflex consists of an elevation in heart rate and vasoconstriction. If reflex pathways are defective, blood pressure falls markedly with hemodynamic pooling. An abnormal response is defined similarly to that associated with standing.

WHO IS A CANDIDATE FOR TESTING?

Autonomic function tests based on changes in heart rate variation and blood pressure regulation can detect cardiovascular complications at early stages of involvement in asymptomatic patients. Because late stages of CAN are indicators of poor prognosis in diabetic patients, early prognostic capabilities offer a significant contribution to diagnosis and subsequent therapy.

Evidence from clinical literature can be found that support recommendations for various subpopulations. They include the following.

Diabetic patients with a history of poor glycemic control

Long-term poor glycemic control can only increase the risk of developing advanced diabetic neuropathy, although long-term follow-up

studies are lacking. A 4-year follow-up study done by Mustonen et al.[42] of 32 individuals with type 2 diabetes showed that poor glycemic control was an important determinant of the progression of autonomic nerve dysfunction.

The DCCT provided extensive clinical evidence that good metabolic control reduces diabetic complications. Specifically with regard to cardiovascular autonomic function, the DCCT showed that intensive glycemic control prevented the development of abnormal heart rate variation and slowed the deterioration of autonomic dysfunction over time for individuals with type 1 diabetes.

Poor glycemic control may also be a consequence of DAN (e.g., gastroparesis that goes unidentified). Treatment of gastro intestinal dysfunction often improves glycemic control.

Diagnosed diabetic patients

Primary prevention of diabetes is the absolute goal. It has been shown that lifestyle intervention can reduce the incidence of type 2 diabetes. Individuals that do develop diabetes, however, are likely to suffer from its complications. In fact, researchers have confirmed the presence of autonomic neuropathy at presentation. In its entirety, the evidence supports the contention that all patients with diabetes, regardless of metabolic control, are at risk for autonomic complications. Given that CAN may be life-threatening and the assessment for its presence can be easily performed, testing for cardiovascular autonomic dysfunction is suggested for individuals with diabetes. This includes

testing to identify children and adolescents with autonomic neuropathy. Massin et al.[43] in his study demonstrated that early puberty is a critical period for the development of CAN and suggested that all type 1 diabetic patients should be screened for CAN beginning at the first stage of puberty.

MANAGEMENT IMPLICATIONS OF CARDIOVASCULAR AUTONOMIC NEUROPATHY

Treatment Interventions for Orthostatic Hypotension

Treatment of orthostatic hypotension comprises nonpharmacological and pharmacological measures. Nonpharmacological measures such as increasing consumption of water[44] and the use of lower-extremity stockings to reduce symptoms (eg, dizziness, dyspnea) should be encouraged when treating orthostatic hypotension attributable to autonomic dysfunction. Pharmacological therapies must balance an increase in standing BP against prevention of supine hypotension. Orthostatic hypotension can be aggravated by different forms of therapy (eg, tricyclic antidepressant [amitriptyline]) used for the treatment of other complications (eg, painful sensory neuropathy). Therefore, careful attention to other medications that may aggravate orthostatic hypotension in these patients is mandatory.[45] Recently, some novel approaches using other pharmacological agents have been investigated in nondiabetic individuals with orthostatic symptoms. Enhancement of ganglionic transmission via the use of pyridostigmine (inhibitor of acetylcholinesterase) improved symptoms and orthostatic BP with only modest effects in supine BP for 15 patients with

POTS.89 Similarly, the use of β-adrenergic blockers may benefit the tachycardia and anticholinergics, the orthostatic bradycardia. Pyridostigmine has also been shown to improve HRV in healthy young adults.[46] Fluoxetine, a selective serotonin reuptake inhibitor, improved hemodynamic parameters and symptoms of orthostatic hypotension in patients with Parkinson disease.[47] In patients with pooling of blood in the splanchnic bed, somatostatin may be of value, and in patients with contracted plasma volume, treatment with erythropoietin is recommended.

Management of Exercise Intolerance

In diabetic individuals with CAN, exercise tolerance is limited as a result of impaired parasympathetic / sympathetic responses that would normally enhance cardiac output and direct peripheral blood flow to skeletal muscles. Reduced ejection fraction, systolic dysfunction, and a decrease in the rate of diastolic filling also limit exercise tolerance. In diabetic patients without evidence of heart disease but with asymptomatic vagal CAN, exercise capacity (greatest tolerable workload and maximal oxygen uptake), heart rate, BP, cardiac stroke volume, and hepatosplanchnic vascular resistance are diminished. A further decrease in exercise capacity and BP is seen in patients with both vagal CAN and orthostatic hypotension. The severity of CAN correlates inversely with the increase in heart rate at any time during exercise and with the maximal increase in heart rate. Thus, CAN contributes to diminished exercise tolerance. Therefore, autonomic testing offers a useful tool

to identify patients with potentially poor exercise performance and may help prevent hazards when patients are introduced to exercise training programs. For diabetic persons likely to have CAN, it has been suggested that cardiac stress testing should be performed before beginning an exercise program. When discussing exercise instructions and goals with patients with CAN, health care providers need to emphasize that the use of heart rate is an inappropriate gauge of exercise intensity, because maximal heart rate is lower in persons with CAN. Recently, it has been shown that percent heart rate reserve, an accurate predictor of percent VO2 reserve, can be used to prescribe and monitor exercise intensity in diabetic individuals with CAN. An alternate method for monitoring intensity of physical activity is the rated perceived exertion scale.

Perioperative Management

There is a 2 to 3-fold increase in cardiovascular morbidity and mortality intraoperatively for patients with diabetes. Patients with severe autonomic dysfunction have a high risk of BP instability,[48] and intraoperative BP support is needed more often in those with greater impairment. Intraoperative hypothermia (which may decrease drug metabolism and affect wound healing) and impaired hypoxic induced ventilatory drive have also been shown to be associated with the presence of CAN. Noninvasive diagnostic methods assessing autonomic function allow identification of at-risk patients preoperatively and may better prepare the anesthesiologist for potential hemodynamic changes.

Potential for Reversal of CAN

Several studies have reported that it is possible to improve HRV. In patients with minimal abnormalities, endurance training under strict supervision and lifestyle intervention associated with weight loss improve HRV. Johnson et al.[49] have reported improved LV function in patients with diabetic autonomic neuropathy (DAN) by using an aldose reductase inhibitor, but this still needs to be shown on a larger scale. Surprisingly, LV ejection fractions improved without a change in quantitative autonomic function test scores. β-Blockers such as bisoprol improved HRV in heart failure.[50] The addition of spironolactone to enalapril, furosemide, and digoxin in patients with heart failure improved sympathovagal balance.[51] Angiotensin-converting enzyme (ACE) inhibition with quinapril increases total HRV and improves the parasympathetic / sympathetic balance in patients with mild but not advanced autonomic neuropathy.[52]

ACE inhibition improves the prognosis of chronic heart failure,[53] but plasma concentrations of angiotensin II remain elevated, which may be related to non-ACE pathways that convert angiotensin 1 to angiotensin II. Hence, addition of an angiotensin receptor blockade may overcome this problem,[54] ostensibly effecting greater blockade of the renin–angiotensin–aldosterone system. Indeed, there are now several reports of beneficial effects on hemodynamic and neurohumoral effects of adding losartan, valsartan, or candesartan to an ACE inhibitor. To investigate the effect of ACE inhibition or

angiotensin receptor blockade and their combination on both DAN and LVDD in asymptomatic patients with diabetes, Didangelos et al.[55] examined 62 patients (34 women) with long-term diabetes mellitus (24 with type 1 diabetes mellitus and DAN).

The patients, who were aged 51.7 ± 13.9 years and were free of coronary artery disease and arterial hypertension at baseline, were studied for a 12-month period. Early ACE inhibition or angiotensin receptor blockade improved both DAN and LVDD after 1 year of treatment in asymptomatic patients with type 1 or 2 diabetes mellitus. The combination may be slightly better than monotherapies on DAN and LVDD, auguring well for the patient with established CAN. The clinical importance of these effects should be validated by larger studies, however. Improvement in glycemic control reduces the incidence of CAN and slows the progression thereof. Glycemic control with a reduction of HbA1c from 9.5 to 8.4 has also been shown to improve HRV with mild autonomic abnormalities; this was not so in cases of advanced autonomic abnormalities.[56]

The use of aldose reductase inhibitors such as sorbinil improved resting and maximum cardiac output, and epalrestat improved MIBG uptake and HRV in patients with mild abnormalities but not in those with advanced CAN.[57] The most salutary lesson, however, derives from the Steno memorial study by Gaede et al.,[58] in which intensive multifactorial management aimed at control of BP, lipids, HBA1c, use of aspirin, vitamins E and C, and ACE inhibitors

reduced CAN by 68%. Thus, it is important to diagnose CAN because the outlook is not as dismal as was once perceived; there are now symptomatic therapies that can reorient the functional abnormalities toward improved function, as well as therapies that provide prospects for reversal.

As mentioned previously, clinicians must be careful when giving recommendations with regard to exercise for individuals with CAN. This does not mean, however, that exercise is inappropriate for individuals with CAN. In fact, Howorka et al.[59] showed that physical training improved heart rate variation in insulin-requiring diabetic individuals with early CAN. Thus, careful testing to evaluate cardiovascular autonomic function and its degree of development is extremely important. Clinicians working together with the patient can develop an appropriate exercise program that will yield a plan for reaping maximum benefits.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY POPULATION

A total of 100 patients satisfying all the inclusion and exclusion criteria were enrolled for the study from the population of Type 2 Diabetes patients who attended the out patient clinics and Inpatients of Medicine, K.A.P.V. Govt. Medical College and Hospital. Written consent was obtained from all the patients participating in the study after clearly explaining the study procedure. Autonomic neuropathy testing by simple bet side tests was done in op department and Medical ward using ECG monitor, Pulseoxymeter and BP apparatus for the same 100 patients.

STUDY DURATION

This study was conducted for a period from May 2010 to August 2011.

STUDY DESIGN

A Cross-sectional study to evaluate the Prevalence of Cardiovascular Autonomic Neuropathy in Type 2 diabetes and correlate it with duration of Diabetes and to investigate the relationship between cardiac autonomic dysfunction and corrected QT interval.

METHODS

Detailed clinical history was taken from each patients and a complete review of their case notes performed. A complete clinical examination of the cardiovascular system was done for each patient.

Tests for autonomic functions

On the day of testing patients were instructed not to ingest caffeine containing products. All recordings the done 5-8 hours post prandially. Blood pressure was recorded manually using standard sphygmomanometer. The heart rate variation was calculation using standard Heart rate monitor, Pulseoxymeter and continuous ECG recording. A baseline ECG was taken with a Standard ECG machine for calculation of QTc interval. The simple bedside tests for assessing the autonomic nervous system were described by Ewing and Clarke. All patients were subjected to a battery of five tests as described below:

Heart rate response to valsalva maneuver

The subject was seated quietly and then asked to blow into the empty barrel of a 20ml syringe attached to a mercury sphygmomanometer, to maintain a pressure of 40 mm Hg for 10 seconds. The ratio of the maximum heart rate during blowing to the minimum during the compensatory bradycardia after stopping is calculated. The maneuver was repeated three times with one minute interval in between and results were expressed as

Valsalva ratio = Max heart rate ÷ Minimum heart rate

The mean of the three-valsalva ratios was taken as the final value.

Heart rate variation during deep breathing

The subject was asked to breathe deeply at six breaths / min (Five seconds “in” and five seconds “out”) for one minute. The average heart rate difference (maximum minus minimum during the respiratory cycle) is

calculated while the patient breaths deeply for 1 min. The results were expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats / min.

Immediate heart rate response to standing

The test was performed with the subject lying quietly on a couch. The heart rate increase is recorded 15 seconds after standing from lying position. Alternatively, the ratio of the R-R interval of the 30th beat after standing to that of the 15^{th} beat ('30:15') can be calculated.

Blood pressure response to standing

This test measured the subject's blood pressure with a sphygmomanometer while he was lying quietly. Then he was made to stand up and the blood pressure again after one minute. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and the systolic pressure standing. The test was in repeated three times and the mean systolic blood pressure was calculated.

Blood pressure response to sustained hand grip

The blood pressure of the patient was taken three times before the maneuver. A modified sphygmomanometer was used to sustain handgrip. The patient was asked to grip the inflatable rubber and apply maximum voluntary pressure possible. A reading from the attached mercury manometer was taken during maximum voluntary contraction. Thereafter, the patient was asked to

maintain 30% of maximum voluntary contraction for as long as possible up to five minutes. Blood pressure was measured at one minute intervals during the handgrip. The result was expressed as the difference between the highest diastolic blood pressure during the handgrip exercise and the mean of the three diastolic blood pressure readings before the handgrip began.

The scoring system was done using the following table and results were analysed.

Score	HRV Test			BP Test	
	Deep breathing	**Valsalva Ratio**	**Response to Standing**	**Response to Handgrip**	**Response to Standing**
0	> 15	> 1.20	> 15	> 15	≤ 10
1	11-15	1.1-1.20	12-15	11-15	11-30
2	≤ 10	≤ 1.10	< 12	≤ 10	> 30

INCLUSION CRITERIA

Type 2 diabetes already on treatment and newly diagnosed patients.

EXCLUSION CRITERIA

1) Age above 60 years
2) Documented ischaemic heart disease
3) Documented valvular or congenital heart disease
4) Hypertension
5) COPD
6) Uraemia
7) Parkinsonism

STATISTICAL ANALYSIS

Statistical analysis was carried out for 100 patients after categorizing each variable – Age, sex, duration of diabetes, autonomic function tests, autonomic dysfunction score, interpretation results and QTc interval were analyzed. The significance of difference between the proportions was indicated by the chi-square (χ^2) statistic. The significance of difference in mean between the groups was calculated by student t-test. Variables were considered to be significant if ($P < 0.05$). Intervariate analysis was done by using Pearson's r-value correlation.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

TABLE - 1

AGE DISTRIBUTION

AGE (in Yrs)	NUMBER
21-30	2
31-40	26
41-50	56
>50	16

More than half of the study population belongs to the age group of 41-50 years (56%).

FIG. 1

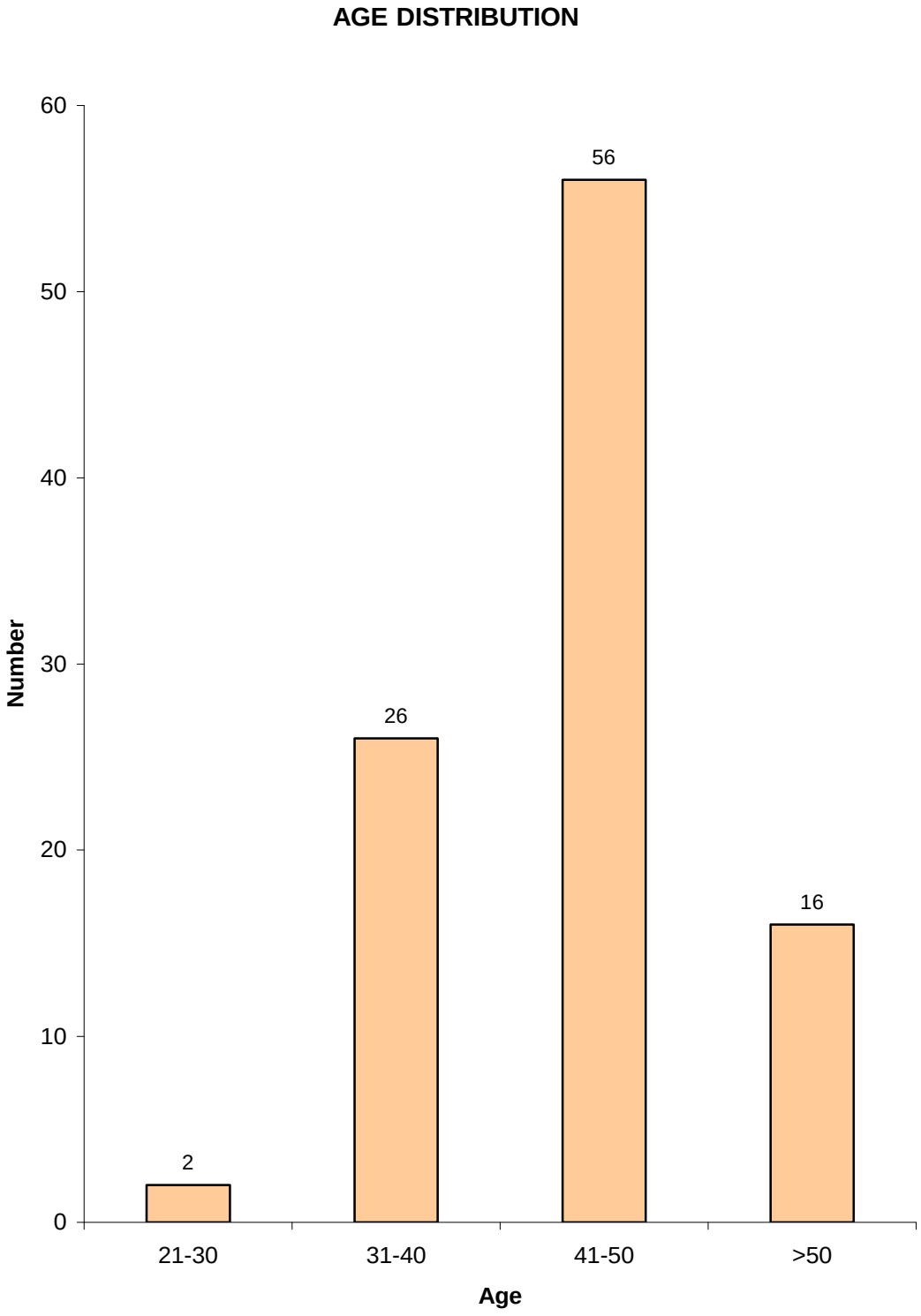

AGE DISTRIBUTION
Number
60
50
40
30
20
10
0
2
26
56
16
21-30
31-40
41-50
>50
Age

TABLE - 2

SEX DISTRIBUTION

Sex	Number
Males	56
Females	44

FIG. 2

SEX DISTRIBUTION

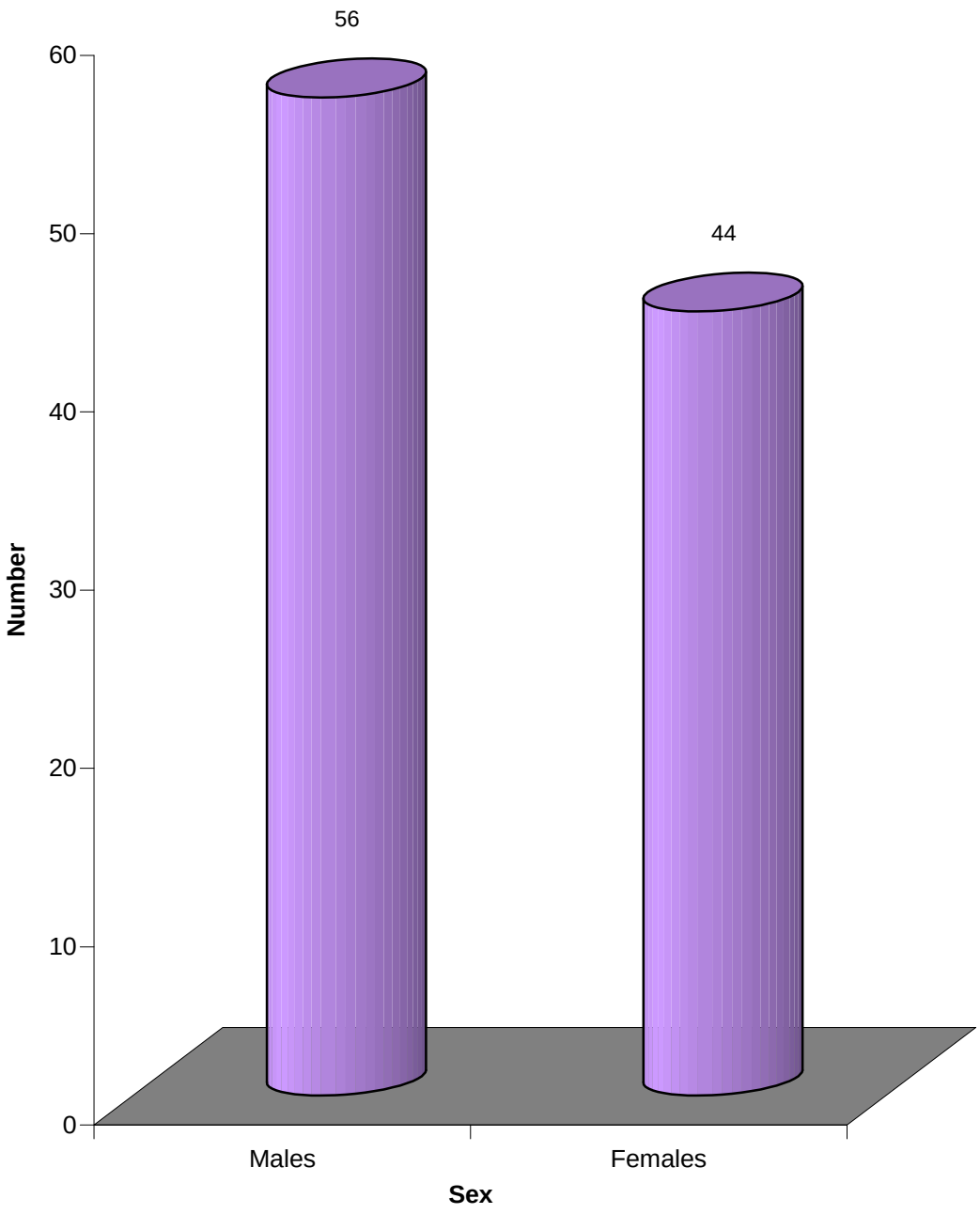


TABLE - 3

DURATION OF DIABETES

DURATION OF DIABETES (YRS)	NO.
0-5	56
6-10	28
> 10	16

More than 50% of the study population has duration of diabetes less than 5 years.

FIG. 3

DURATION OF DIABETES

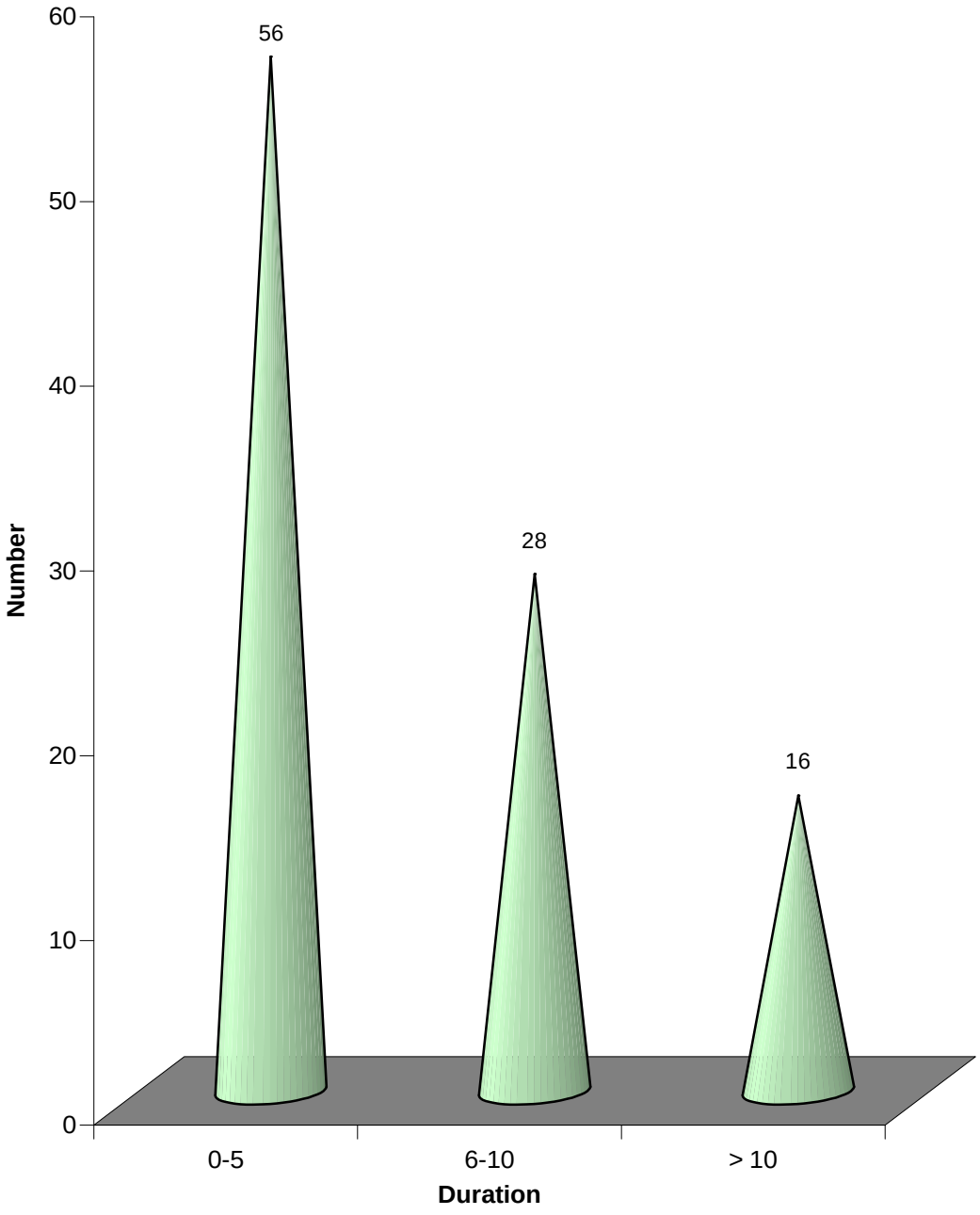


TABLE - 4

CARDIOVASCULAR AUTONOMIC DYSFUNCTION - FREQUENCY DISTRIBUTION OF NORMAL (0-1), BORDERLINE (2-4), ABNORMAL (≥5) – CAN SCORE

CAN SCORE	NUMBER
0-1	58
2-4	21
> 5	21

FIG. 4

CARDIOVASCULAR AUTONOMIC DYSFUNCTION - FREQUENCY DISTRIBUTION OF NORMAL (0-1), BORDERLINE (2-4), ABNORMAL (≥5) – CAN SCORE

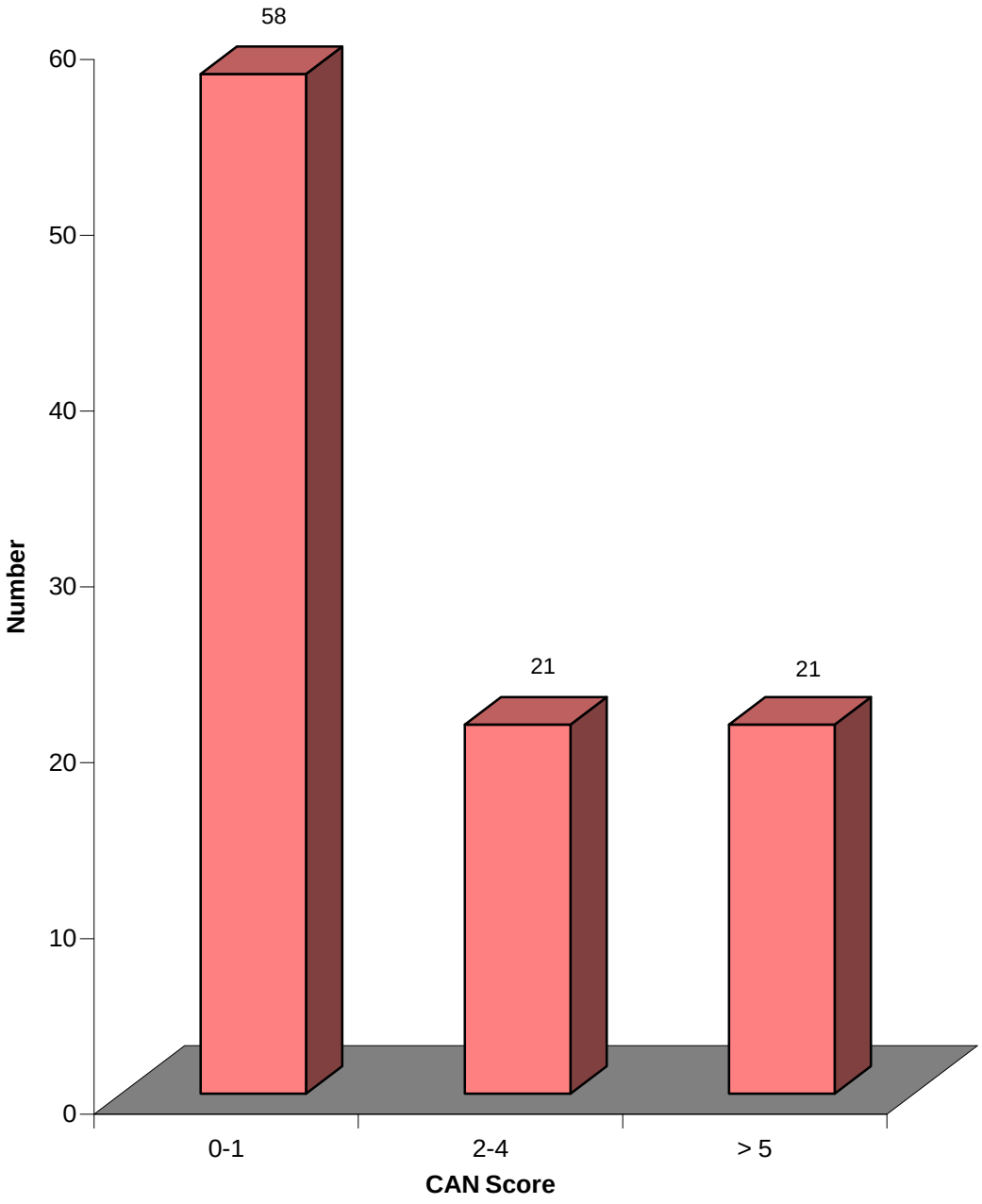


TABLE – 5

HRV TO DEEP BREATHING

VARIABILITY	NUMBER
< 10	33
11-15	18
>15	49

Correlation coefficient r = (-0.713) (comparing heart rate variability to deep breathing with CAN Score)

R square = 0.4969

P < 0.0001 - Highly significant

FIG. 5

HRV TO DEEP BREATHING

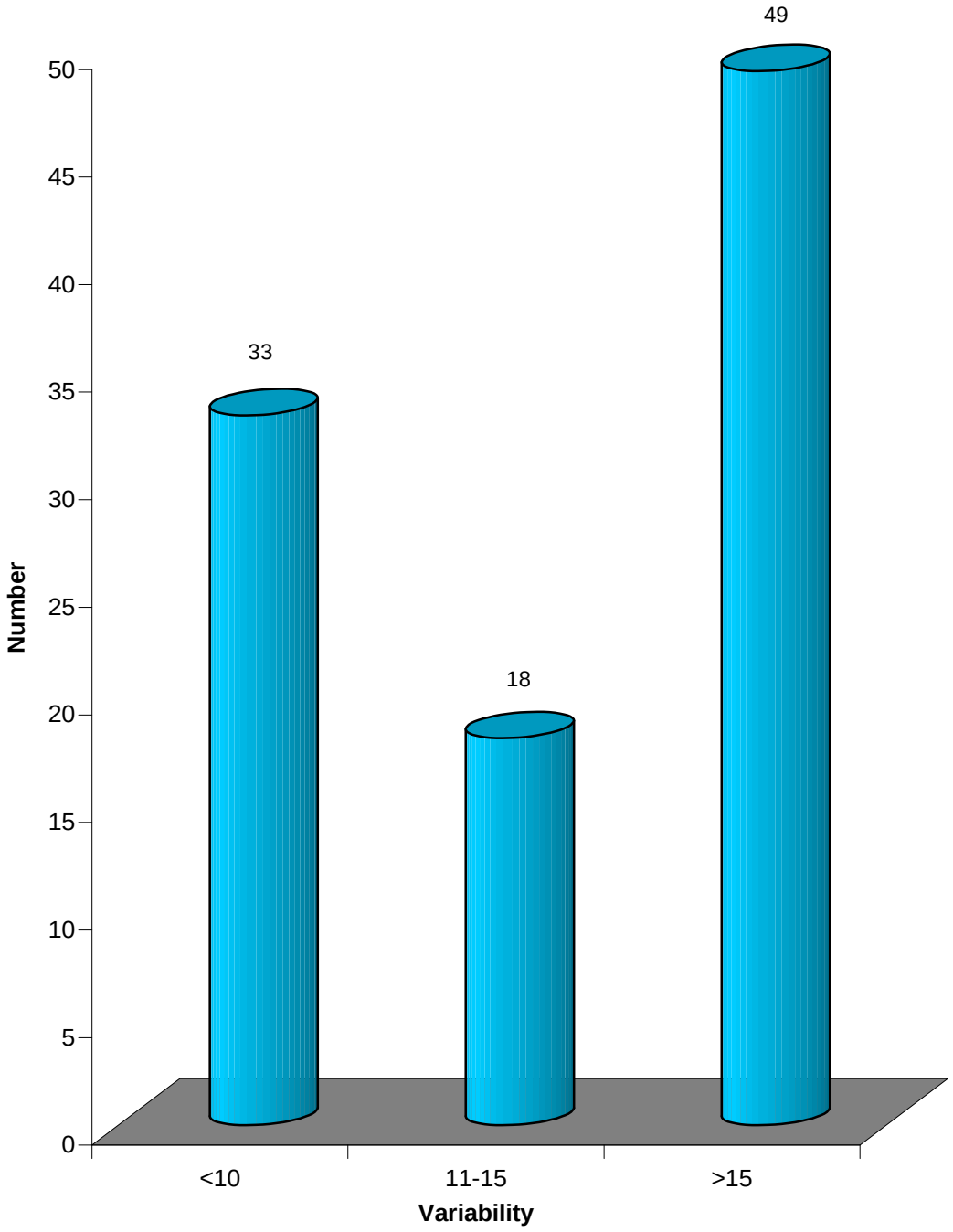


TABLE -6

HRV TO STANDING

VARIABILITY	NUMBER
<12	37
12 - 15	11
>15	52

Correlation coefficient r = (-0.85) (comparing heart rate variability to standing with CAN Score)

R square = 0.7067

P < 0.0001 - Highly significant

FIG. 6

HRV TO STANDING

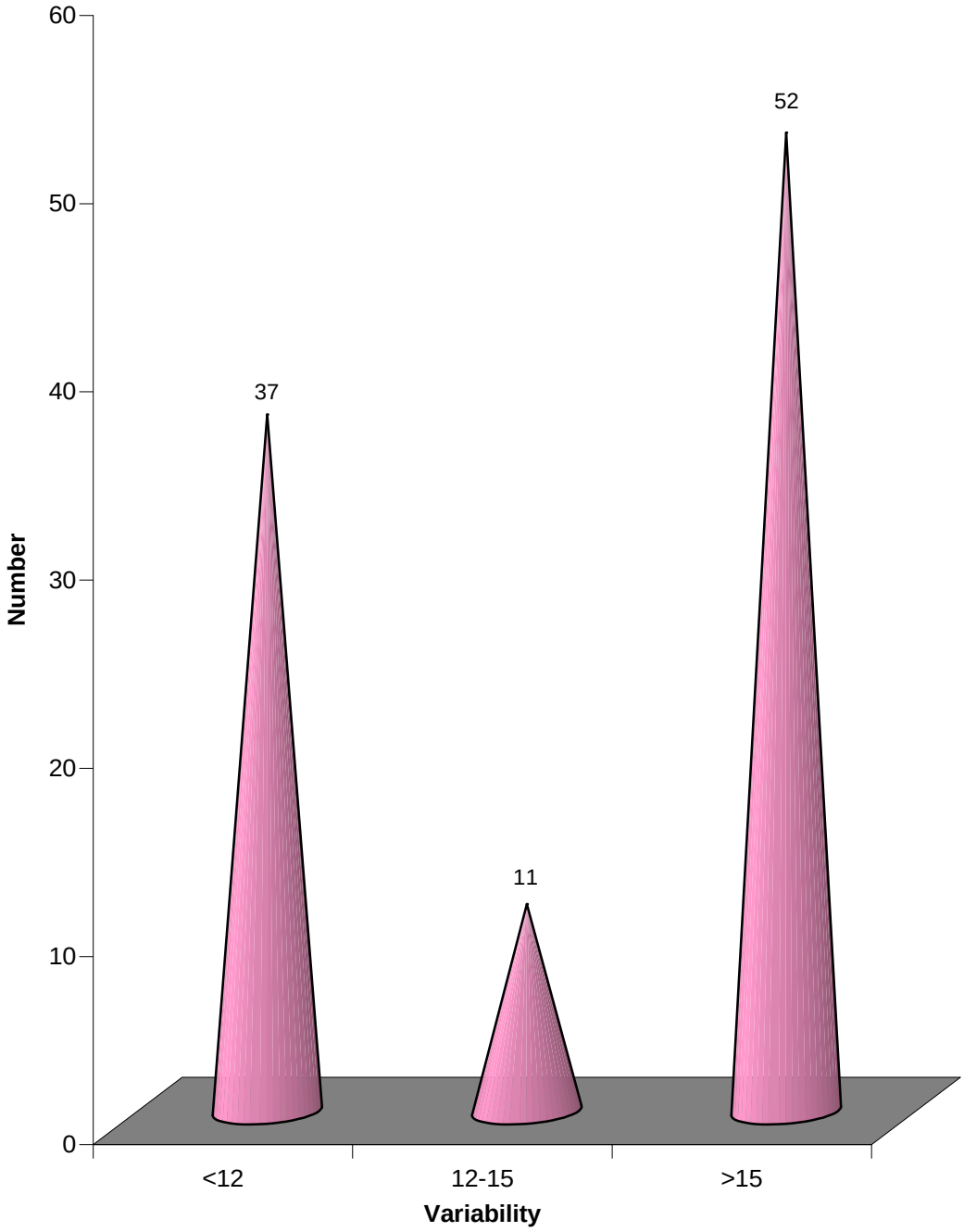


TABLE - 7

CARDIOVASCULAR AUTONOMIC DYSFUNCTION – FREQUENCY DISTRIBUTION OF NORMAL (0-1), BORDERLINE (2-4), ABNORMAL (≥5) – COMPARISON WITH DURATION OF DIABETES MELLITUS

CAN SCORE	GROUP						Statistical Interference 'p'
	< 5 Yrs		6-10 Yrs		> 10 Yrs		
	n	%	n	%	n	%	
0-1	40	72	14	50	4	26	0.001
2-4	11	20	7	25	3	16	0.000
≥ 5	5	8	7	25	9	58	0.002
TOTAL	**56**	**100**	**28**	**100**	**16**	**100**	**0.001**

In the study population, the prevalence of definite CAN was 8%, 24% and 58% in group A, B and C respectively. The prevalence of definite CAN increases with increase in duration of diabetes. P value < 0.001 significant.

FIG. 7

CARDIOVASCULAR AUTONOMIC DYSFUNCTION – FREQUENCY DISTRIBUTION OF NORMAL (0-1), BORDERLINE (2-4), ABNORMAL (≥5) – COMPARISON WITH DURATION OF DIABETES MELLITUS

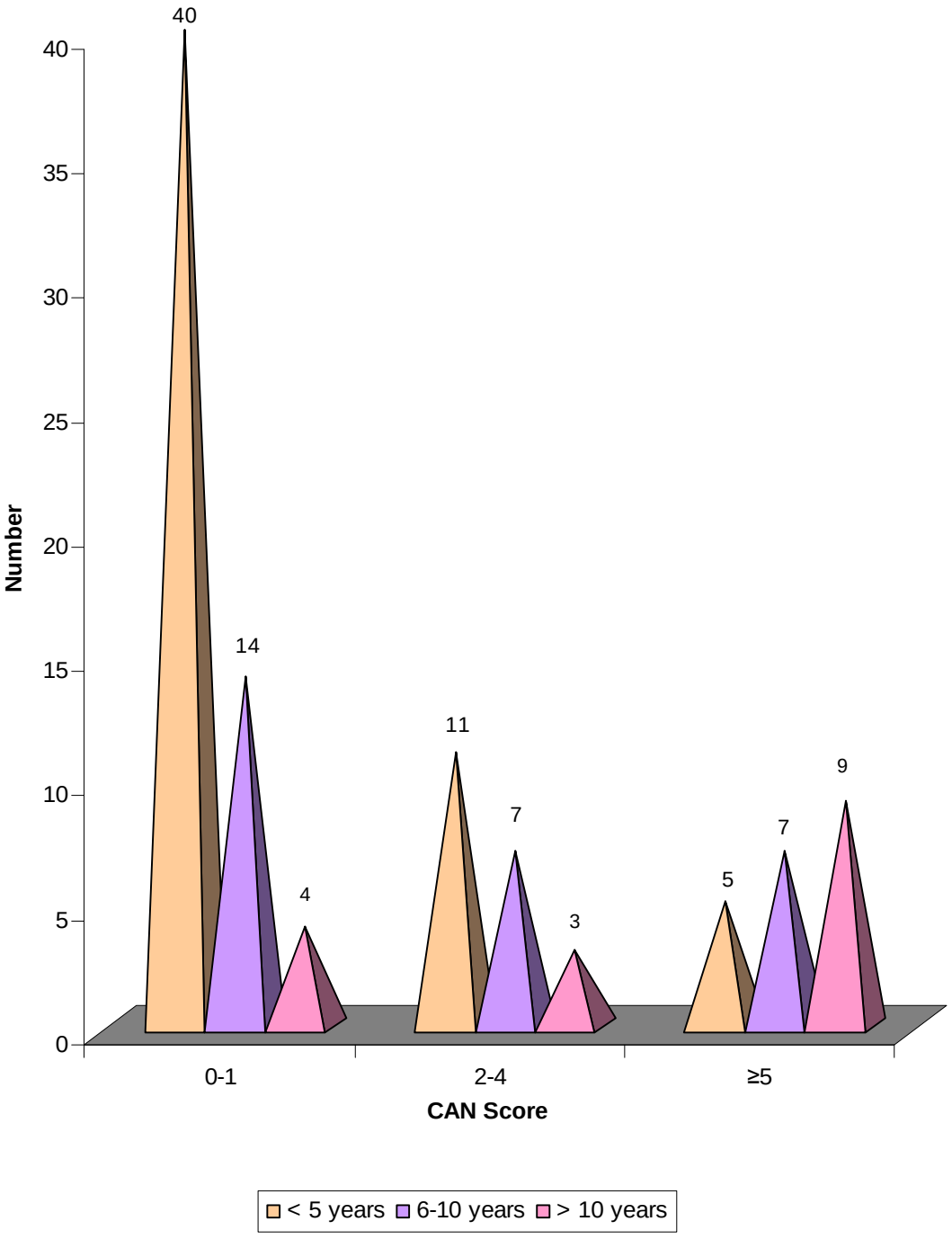


TABLE - 8

CORRELATION BETWEEN QTC AND CAN SCORE

QTc	CAN negative	CAN Positive
< 440	61	4
> 440	18	17

Sensitivity : 77%

Specificity : 81%

PPV : 93.85%

Pearson’s correlation coefficient (r) =0.53

SIGNIFICANT RELATIONSHIP

P value: < 0.0001 VERY HIGHLY SIGNIFICANT

FIG. 8

CORRELATION BETWEEN QTC AND CAN SCORE

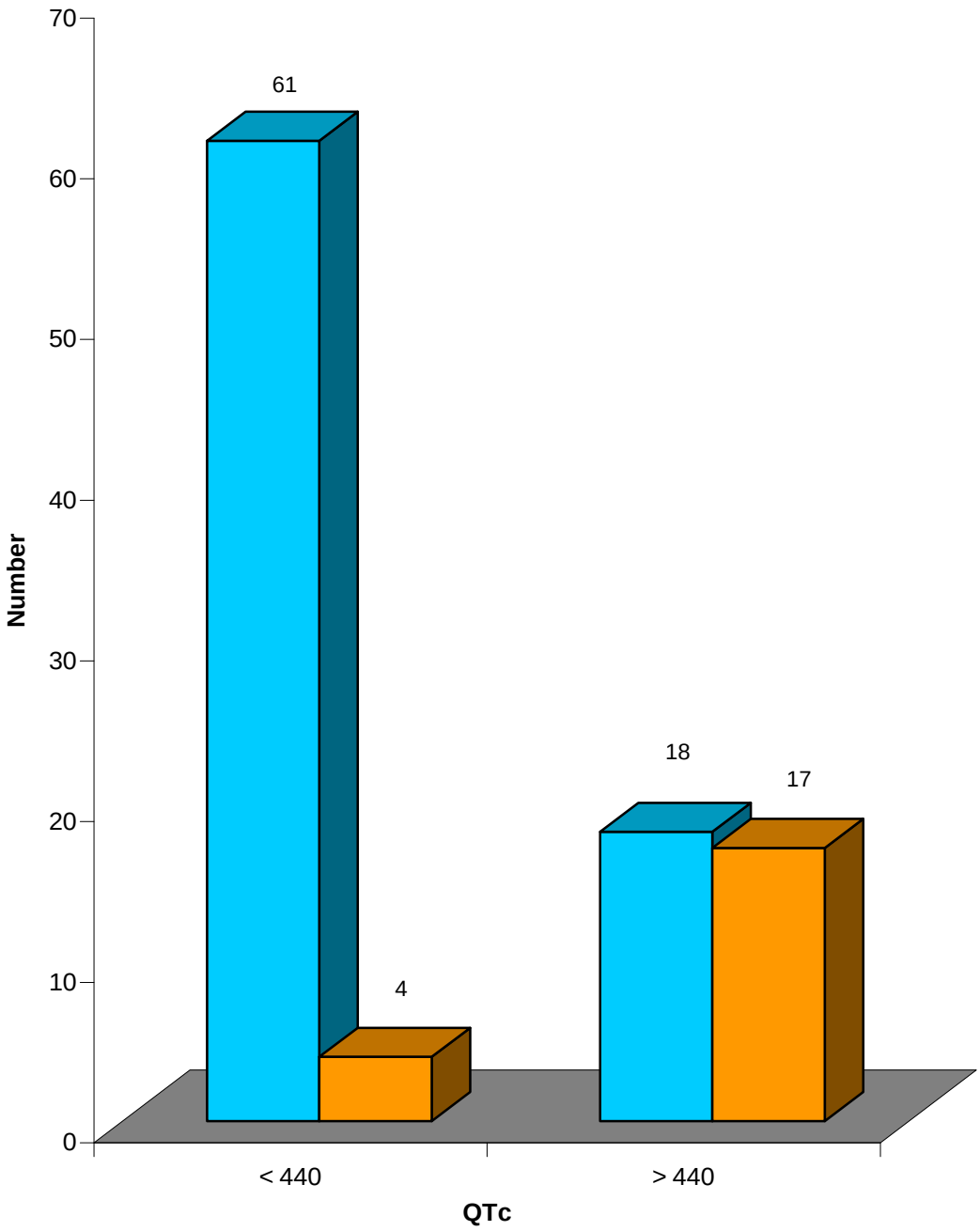


TABLE – 9

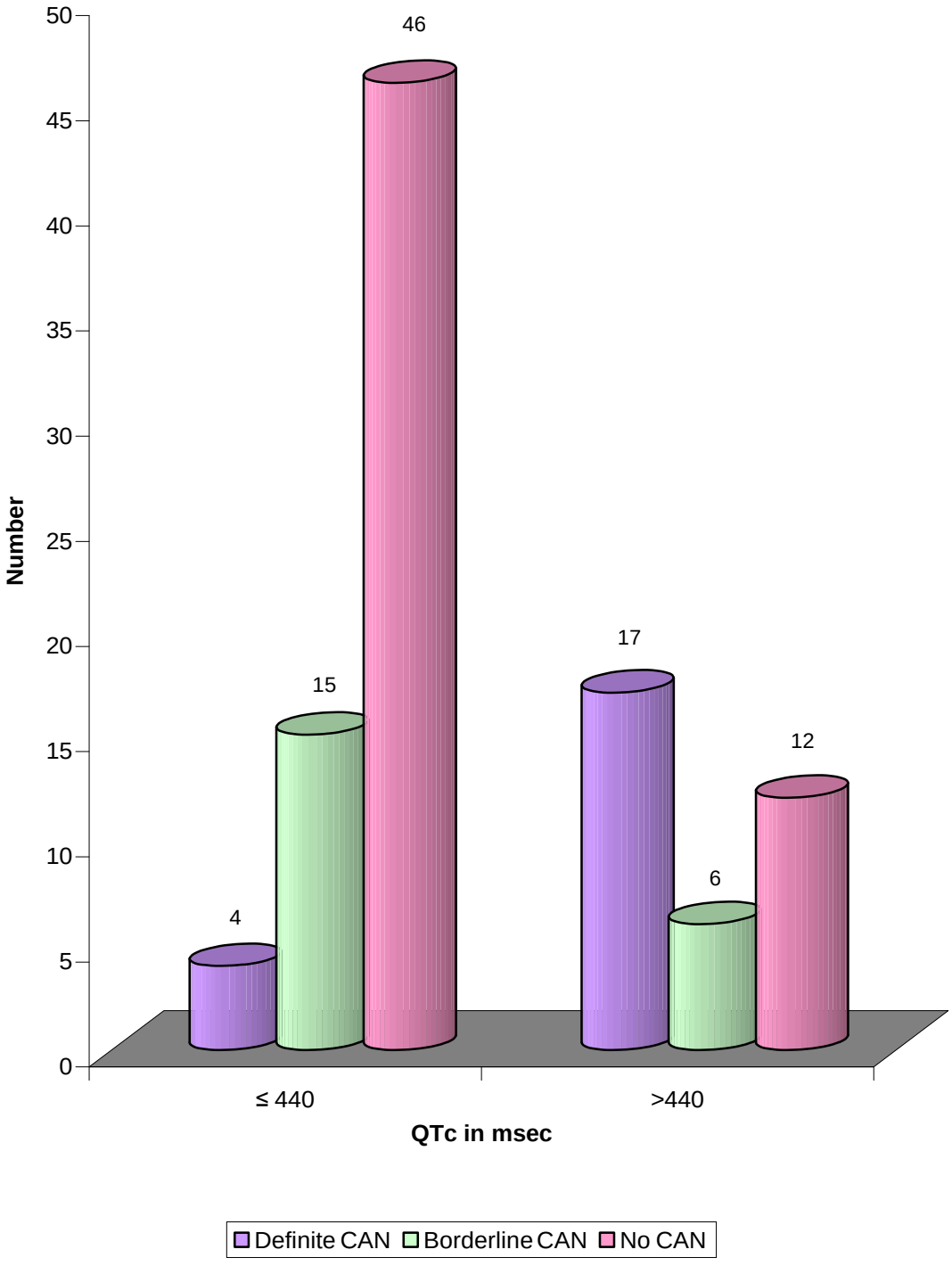
CORRELATION BETWEEN AUTONOMIC NEUROPATHY (AN) AND QTc PROLONGATION IN TOTAL DIABETIC PATIENTS

QTc in msec	Definite CAN	%	Borderline CAN	%	No CAN	%	'p' Value
≤ 440	4	20	15	68.8	46	79.5	0.001
>440	17	80	6	31.2	12	20.5	0.041

From the table, QTc interval prolongation occurs with development of CAN. Prolongation of QTc interval is well correlated with Cardiac Autonomic Neuropathy - P value < 0.001.

FIG. 9

CORRELATION BETWEEN AUTONOMIC NEUROPATHY (AN) AND QTc PROLONGATION IN TOTAL DIABETIC PATIENTS



DISCUSSION

DISCUSSION

This study was done in a subgroup of south Indian population to find the prevalence of cardiac autonomic neuropathy in diabetic patients and to find out the relationship between CAN and prolonged QTc interval.

More than half of the study population belongs to the age group of 41-50 years (56%).

There were 56 males and 44 females in the study and there was no significant relationship between sex and cardiac autonomic neuropathy. With regard to whether either sex is more likely to develop autonomic dysfunction, the literature has revealed conflicting reports. For example, in the DCCT, the presence of autonomic neuropathy correlated with male sex along with age and duration. Jaffe et al.[60] show male sex to be predictive of depressed HRV in addition to age, duration, and retinopathy. However, in another study of type 1 diabetic individuals, females along with other parameters (e.g., lipids and hypertension) were found to be independent determinants of autonomic dysfunction. May et al.[61] showed a significantly reduced E:I ratio for females in a random sample of 120 type 1 diabetic individuals, along with older age, longer duration, and elevated glucose, triglycerides, blood pressure, and urinary albumin excretion.

In our study those who had diabetes of less than 5 yrs had low prevalence of autonomic dysfunction than those who had diabetes for more than 10 yrs and there was a significant correlation with the duration of diabetes and cardiac autonomic neuropathy.

Significant correlations were observed between autonomic neuropathy and duration of diabetes ($P < 0.0001$) in the EURODIAB IDDM complications study.

In our study, there was a negative pearson co efficient between heart rate variability and CAN score which was also statistically significant.

The study done by Arati et al. HRV was measured in 50 diabetic subjects and 20 normal subjects in the age group of 50 to 70 years. The result showed that diabetic patients had a statistically lower HRV compared to the healthy controls. The result correlates with previous studies of Wheeler and Watkins in 1973 who observed that diabetics have a marked reduction of HRV when compared with normal subjects (Schroeder EB, et al. 2005). This observation has been confirmed subsequently by many others (Vinik AI, et al. 2003).

Diabetes is an organic disorder in which several of changes takes place in the body. The pathophysiology involves almost all the tissues. The autonomic nerves being affected by diabetes mellitus shows the signs of neuropathy. This could be the cause for the altered autonomic control on the heart in chronic diabetics. The lower HRV in severe diabetes could point out at the higher neuropathic damage in such patients. Low HRV is reportedly associated with cardiovascular morbidity and mortality. Therefore diabetics are more susceptible to heart attacks and death due to cardiovascular disorders. Schroeder and coworkers investigated the consequence of diabetes and pre

diabetic metabolic impairments on the 9 year change in heart rate variability and observed that diabetic subjects had a rapid decrease in HRV than non-diabetic subjects and they also found cross sectional associations between decreased HRV and diabetics (Schroeder EB, et al. 2005).

Measurement of heart rate response to deep breathing may allow evaluation of autonomic function in a simple, quick and non-invasive way in general practice.

In our study there was a significant correlation between prolonged QTc interval and cardiac autonomic neuropathy. The Sensitivity was 77%, specificity was 81% and the positive predictive value was 93.85%.

Pappachan J.M. et al.[62] studied the utility of prolongation of corrected QT interval (QTc) in the ECG to diagnose CAN in patients with diabetes. They calculated the sensitivity and specificity of QTc prolongation for the diagnosis of CAN were 77% and 62.5% in type 1 and 76.5% and 75% in type 2, respectively. They concluded that QTc interval in ECG can be used to diagnose CAN with reasonable sensitivity and specificity. This value of sensitivity and specificity correlates with our study.

C.P. Mathur et al.[63] studied 50 patients with diabetes with 20 normal controls to understand the relationship to CAN with QTc interval. There were 15 (78.94%) cases with QTc prolongation out of 19 diabetics with CAN. None of the diabetics without CAN or control subjects had QTc prolongation. It was observed to have sensitivity of 82.6% which is comparable with our study.

A Pourmoghaddas, et al.[64] found that the prevalence of prolonged QTc interval was significantly higher in the case group in comparison with the control group, 8 vs. 2% respectively (p value = 0.012, OR = 4.3).

Abnormality of parasympathetic nervous system is more common than (3 fold) abnormality in sympathetic nervous system.

Mathur et al.[65] found that QTc prolongation in diabetic subjects stands favourably as an autonomic dysfunction parameter as compared to other ANF tests. Further, QTc prolongation has linear positive correlation with the degree of CAN. QTc prolongation in diabetics with an otherwise normal heart can be used as a diagnostic test for assessment of cardiac autonomic neuropathy and may even be considered as a cardiac autonomic function test with prognostic significance.

An association between abnormally prolonged QT interval and syncope, malignant ventricular arrhythmias and sudden cardiac death has been found in various idiopathic and acquired disorders. QT interval prolongation has been implicated in the origin of ventricular arrhythmias, possibly because of less uniform recovery of ventricular excitability in the setting of regional differences in cardiac sympathetic nervous system activity.

Hisayoshi Oka et al.[66] in 1995, attempted to clarify the relationship of the QTc interval to α and β sympathetic as well as parasympathetic function tests and concluded that QTc prolongation is an indicator of cardiac dysautonomia.and found that the QT interval in diabetics was 420 msec v/s 385 msec in nondiabetics and thus was significant.

LIMITATIONS

There were certain limitations in this study:

Newer techniques for measuring autonomic functions like the computer aided power spectral analysis of heart-rate variability could not be done because of limitations in resources and cost.

There was no facility for measuring Serum Magnesium and Calcium which may alter QT interval.

No Holter monitoring facility was available to assess the risk of ventricular tachycardia in patients with QTc prolongation.

It was not possible to rule out the possibility of congenital long QT syndrome.

CONCLUSION

CONCLUSION

The following are the conclusions from this study:

1. The Prevalence of Cardiovascular Autonomic Neuropathy is high in type 2 diabetics in our hospital.
2. The prevalence of CAN will increase with increase in the duration of diabetes. About half of the patients with type 2 diabetes have autonomic dysfunction after ten years.
3. There was a significant correlation between reduced heart rate variability and cardiac autonomic neuropathy.
4. A significant correlation is present between Cardiovascular autonomic dysfunction and QTc prolongation. QTc interval in the ECG can be used to diagnose Cardiovascular autonomic neuropathy with a reasonable sensitivity and specificity.

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ANNEXURE

PATIENT CONSENT FORM

STUDY DETAIL: DIAGNOSTIC ACCURACY OF CORRECTED QT INTERVAL AS SURROGATE MARKER IN DIABETES MELLITUS PATIENTS WITH CARDAC AUTONOMIC NEUROPATHY

Study Centre : Annal Gandhi Memorial Government Hospital, Trichy.

Name of the patient :

Age / Sex :

Identification Number :

Patient / Legal representative may check (✓) these boxes

- I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐
- I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐
- I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my ☐

identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

- I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐
- I hereby consent to participate in this study. ☐
- I hereby give permission to undergo complete clinical examination and diagnostic tests. ☐

Signature / thumb impression of the Patient/Legal Representative:

Name and Address:

Place: **Date:**

Signature of investigator :

Name

Place: **Date:**

PROFORMA

1. Name :

2. Age :

3. Sex :

4. Address :

5. OP/IP No. :

6. Age of onset of diabetes :

7. Duration of diabetes :

8. Treatment history :

9. H/o smoking :

10. H/o alcoholism :

11. H/o anginal pain :

12. Dietary habits :

VITALS

Pulse rate : / min

Blood Pressure : / mm Hg Limb: RUL / LUL

Posture : Standing / Sitting / Supine

Respiratory rate :

ANTHROPOMETRY

Height : m

Weight : kg

BMI : kg / m^2

CVS :

Respiratory system :

Abdomen examination :

CNS examination :

TESTS FOR CARDIO VASCULAR AUTONOMIC FUNCTION

		TEST 1	***TEST 2***	***TEST 3***	***MEAN***
(i)	Valsalva Ratio				
(ii)	Deep Breathing Test				
(iii)	Supine to standing				
(iv)	BP Response to standing				
(v)	BP Response to sustained hand grip				

ECG

QTc :

MASTER CHART

S. NO.	ID.N0	AGE (Yrs)	SEX	OP/IP NO	DURATION OF DIABETES (Yrs)	PULSE RATE (bpm)	BP (mm Hg)	VALSALVA RATIO	HRV TO DEEP BREATHING	DIFFERENCE	HRV FROM SUPINE TO STANDING	DIFFERENCE	BP RESPONSE TO STANDING	BP RESPONSE TO SUSTAINED HAND GRIP	CAN SCORE	QT c
1	ABCD 1	46	M	512	4	82	120/80	1.23	94	12	86	4	126/82	124/84	5	424
2	ABCD 2	55	F	122	5	92	118/70	1.26	105	13	96	4	110/76	100/70	5	452
3	ABCD 3	35	F	597	2	98	120/76	1.38	105	7	100	2	116/80	124/90	3	442
4	ABCD 4	57	M	508	6	75	130/80	1.08	81	6	78	3	120/76	140/90	7	448
5	ABCD 5	59	F	104	20	64	144/66	1.11	68	4	66	2	158/66	150/60	9	462
6	ABCD 6	45	F	624	15	78	120/60	1.14	86	8	81	3	120/70	128/60	7	448
7	ABCD 7	52	F	557	2	115	130/80	1.41	131	16	119	4	130/80	140/90	6	454
8	ABCD 8	54	M	359	2	94	136/84	1.26	105	11	105	11	130/90	148/90	4	426
9	ABCD 9	60	F	586	1	88	100/50	1.13	98	10	92	4	100/60	110/70	4	416
10	ABCD 10	51	F	632	13	100	130/90	1.23	112	12	108	8	142/90	144/100	5	448
11	ABCD 11	56	F	544	6	103	118/80	1.12	110	7	107	4	120/80	120/84	7	458
12	ABCD 12	47	M	638	12	84	130/90	1.17	90	6	92	8	116/80	140/104	7	462
13	ABCD 13	42	M	785	6	88	100/70	1.13	97	9	106	18	100/68	110/86	3	448
14	ABCD 14	33	F	645	3	84	110/74	1.24	98	14	102	18	110/70	120/94	1	412
15	ABCD 15	48	M	348	5	70	110/70	1.22	88	18	90	20	110/70	120/92	0	422
16	ABCD 16	44	M	435	9	92	120/74	1.38	99	7	100	8	116/82	124/90	4	422
17	ABCD 17	55	M	324	4	78	130/80	1.26	96	18	91	13	126/80	140/96	1	418
18	ABCD 18	44	F	455	15	70	120/80	1.11	74	4	72	2	110/70	130/92	6	416
19	ABCD 19	42	M	564	3	80	120/70	1.17	96	16	98	18	110/68	124/86	1	426
20	ABCD 20	42	F	398	8	74	130/82	1.17	90	16	91	17	130/78	130/96	2	442
21	ABCD 21	48	F	567	5	78	130/80	1.26	96	18	91	13	126/80	140/96	1	432
22	ABCD 22	36	M	897	12	68	120/70	1.14	76	8	72	4	110/70	120/80	7	452
23	ABCD 23	58	M	836	7	80	120/70	1.18	96	16	96	16	110/68	124/86	1	430
24	ABCD 24	45	F	534	4	94	136/84	1.26	105	11	105	11	130/90	148/90	4	428
25	ABCD 25	48	M	509	3	70	110/70	1.22	86	16	89	19	110/70	120/88	0	431
26	ABCD 26	39	M	672	6	80	120/70	1.18	96	16	98	18	110/70	124/86	1	423

S. NO.	ID.N0	AGE (Yrs)	SEX	OP/IP NO	DURATION OF DIABETES (Yrs)	PULSE RATE (bpm)	BP (mm Hg)	VALSALVA RATIO	HRV TO DEEP BREATHING	DIFFERENCE	HRV FROM SUPINE TO STANDING	DIFFERENCE	BP RESPONSE TO STANDING	BP RESPONSE TO SUSTAINED HAND GRIP	CAN SCORE	QT c
27	ABCD 27	45	M	345	14	80	130/80	1.16	86	6	88	8	120/78	140/92	6	426
28	ABCD 28	47	F	458	2	84	110/74	1.24	96	12	102	18	110/70	120/90	1	433
29	ABCD 29	32	M	784	8	70	110/70	1.22	88	18	86	16	106/70	120/90	0	432
30	ABCD 30	43	F	670	11	74	130/82	1.17	90	16	91	17	130/78	130/96	2	424
31	ABCD 31	35	M	643	1	84	110/74	1.24	96	12	102	18	110/70	120/90	1	420
32	ABCD 32	46	F	834	6	70	120/80	1.11	74	4	72	2	110/70	130/92	6	452
33	ABCD 33	31	M	692	2	84	110/74	1.24	96	12	102	18	110/70	120/90	1	446
34	ABCD 34	28	M	340	1	74	130/82	1.17	90	16	91	17	130/78	130/96	2	426
35	ABCD 35	52	M	684	12	80	120/70	1.18	97	17	96	16	110/70	124/86	1	418
36	ABCD 36	56	M	549	7	92	120/74	1.38	99	7	100	8	116/82	124/90	4	446
37	ABCD 37	44	M	810	3	84	110/74	1.24	96	12	102	18	110/70	120/90	1	428
38	ABCD 38	36	M	954	3	70	110/70	1.24	86	16	88	18	110/70	120/90	0	448
39	ABCD 39	38	F	837	4	80	120/70	1.17	96	16	98	18	110/68	124/86	1	436
40	ABCD 40	41	M	497	9	84	110/74	1.24	98	14	102	18	110/70	120/94	1	426
41	ABCD 41	41	F	237	15	78	120/76	1.14	84	6	87	9	110/70	130/90	6	424
42	ABCD 42	36	M	354	2	70	110/70	1.22	86	16	89	19	110/70	120/88	0	446
43	ABCD 43	58	F	498	5	84	110/74	1.24	96	12	102	18	110/70	120/90	1	428
44	ABCD 44	58	M	453	6	78	130/80	1.24	98	20	92	14	126/80	140/96	1	432
45	ABCD 45	32	F	637	18	88	110/80	1.16	92	4	96	8	100/76	120/94	6	458
46	ABCD 46	45	M	659	4	84	110/74	1.24	96	12	102	18	110/70	120/90	1	444
47	ABCD 47	48	F	854	9	75	130/80	1.08	81	6	78	3	130/76	144/90	7	454
48	ABCD 48	33	M	643	2	80	120/70	1.17	96	16	98	18	110/68	124/86	1	436
49	ABCD 49	45	F	733	8	92	120/74	1.38	99	7	100	8	116/82	124/90	4	448
50	ABCD 50	48	F	593	5	84	110/74	1.24	86	2	92	8	110/70	120/90	1	442
51	ABCD 51	47	M	742	5	78	130/80	1.26	96	18	91	13	126/80	140/96	1	422
52	ABCD 52	56	M	890	7	70	110/70	1.22	88	18	90	20	110/70	120/92	0	416

S. NO.	ID.N0	AGE (Yrs)	SEX	OP/IP NO	DURATION OF DIABETES (Yrs)	PULSE RATE (bpm)	BP (mm Hg)	VALSALVA RATIO	HRV TO DEEP BREATHING	DIFFERENCE	HRV FROM SUPINE TO STANDING	DIFFERENCE	BP RESPONSE TO STANDING	BP RESPONSE TO SUSTAINED HAND GRIP	CAN SCORE	QT c
53	ABCD 53	38	F	957	18	80	120/84	1.19	84	4	90	10	110/80	130/96	3	424
54	ABCD 54	32	M	874	1	78	130/80	1.26	96	18	91	13	126/80	140/96	1	418
55	ABCD 55	46	F	674	6	84	110/74	1.24	98	14	102	18	110/70	120/94	1	452
56	ABCD 56	48	M	693	4	88	100/70	1.13	97	9	106	18	100/68	110/86	3	444
57	ABCD 57	45	M	489	3	84	110/74	1.24	96	12	102	18	110/70	120/90	1	432
58	ABCD 58	42	M	769	2	80	120/70	1.18	96	16	96	16	110/68	124/86	1	422
59	ABCD 59	42	F	701	14	92	120/74	1.38	99	7	100	8	116/82	124/90	3	426
60	ABCD 60	43	M	492	9	103	118/80	1.12	110	7	107	4	120/80	120/84	7	448
61	ABCD 61	45	F	307	4	84	110/74	1.24	86	2	92	8	110/70	120/90	1	418
62	ABCD 62	38	M	636	3	78	120/76	1.14	84	6	87	9	110/70	130/90	6	452
63	ABCD 63	49	F	665	15	78	130/80	1.26	96	18	91	13	126/80	140/96	1	448
64	ABCD 64	49	M	987	8	76	110/74	1.23	92	16	94	18	106/70	110/96	1	426
65	ABCD 65	42	M	765	2	78	130/80	1.26	96	18	91	13	126/80	140/96	1	418
66	ABCD 66	48	M	873	4	80	120/70	1.18	96	16	96	16	110/68	124/86	1	422
67	ABCD 67	37	F	902	6	70	110/70	1.22	86	16	88	18	110/70	120/90	0	436
68	ABCD 68	33	M	761	1	70	110/70	1.22	86	16	89	19	110/70	120/88	0	446
69	ABCD 69	45	M	392	18	84	110/74	1.24	96	12	102	18	110/70	120/90	1	416
70	ABCD 70	44	F	739	3	80	120/70	1.18	96	16	96	16	110/68	124/86	1	424
71	ABCD 71	50	M	843	8	80	130/80	1.16	86	6	88	8	120/78	140/92	6	458
72	ABCD 72	42	F	456	2	80	120/70	1.18	97	17	96	16	110/70	124/86	1	422
73	ABCD 73	37	M	721	6	76	110/74	1.23	90	14	94	18	106/70	110/92	1	432
74	ABCD 74	49	M	429	5	80	120/70	1.18	97	17	96	16	110/70	124/86	1	444
75	ABCD 75	33	F	465	3	70	11//76	1.23	86	16	89	19	110/70	120/88	0	416
76	ABCD 76	36	M	842	2	78	130/80	1.26	96	18	91	13	126/80	140/96	1	422
77	ABCD 77	48	F	683	9	74	130/82	1.17	90	16	91	17	130/78	130/96	2	414
78	ABCD 78	44	F	640	4	80	120/70	1.17	96	16	98	18	110/68	124/86	1	426

S. NO.	ID.N0	AGE (Yrs)	SEX	OP/IP NO	DURATION OF DIABETES (Yrs)	PULSE RATE (bpm)	BP (mm Hg)	VALSALVA RATIO	HRV TO DEEP BREATHING	DIFFERENCE	HRV FROM SUPINE TO STANDING	DIFFERENCE	BP RESPONSE TO STANDING	BP RESPONSE TO SUSTAINED HAND GRIP	CAN SCORE	QT c
79	ABCD 79	42	M	805	2	80	120/84	1.19	84	4	90	10	110/80	130/96	3	412
80	ABCD 80	43	F	786	22	76	110/74	1.23	90	14	94	18	106/70	110/92	1	428
81	ABCD 81	46	M	654	6	80	120/70	1.18	97	17	96	16	110/70	124/86	1	432
82	ABCD 82	48	F	666	5	78	130/80	1.26	96	18	91	13	126/80	140/96	1	418
83	ABCD 83	34	M	386	3	78	110/80	1.14	98	20	96	18	110/68	124/86	1	442
84	ABCD 84	27	M	333	8	70	110/70	1.22	86	16	89	19	110/70	120/88	0	426
85	ABCD 85	56	F	308	5	78	130/80	1.26	96	18	91	13	126/80	140/96	1	422
86	ABCD 86	37	F	620	2	80	120/70	1.18	97	17	96	16	110/70	124/86	1	424
87	ABCD 87	45	M	689	2	92	120/74	1.38	99	7	100	8	116/82	124/90	4	426
88	ABCD 88	45	F	679	3	92	120/74	1.38	99	7	100	8	116/82	124/90	3	420
89	ABCD 89	38	M	502	3	74	130/82	1.17	90	16	91	17	130/78	130/96	2	416
90	ABCD 90	42	M	239	6	84	110/74	1.24	86	2	92	8	110/70	120/90	1	410
91	ABCD 91	32	F	678	1	80	120/70	1.18	97	17	96	16	110/70	124/86	1	448
92	ABCD 92	47	M	321	4	70	110/70	1.22	86	16	88	18	110/70	120/90	0	417
93	ABCD 93	44	F	397	7	78	130/80	1.26	96	18	91	13	126/80	140/96	1	418
94	ABCD 94	38	F	278	3	92	120/74	1.38	99	7	100	8	116/82	124/90	3	418
95	ABCD 95	44	M	481	4	80	130/80	1.16	86	6	88	8	120/78	140/92	6	452
96	ABCD 96	45	M	909	3	80	120/70	1.18	96	16	98	18	110/70	124/86	1	424
97	ABCD 97	35	F	691	9	74	130/82	1.17	90	16	91	17	130/78	130/96	2	422
98	ABCD 98	42	M	639	2	70	110/70	1.24	86	16	88	18	110/70	120/90	0	426
99	ABCD 99	42	F	425	4	80	120/70	1.18	96	16	96	16	110/68	124/86	1	444
100	ABCD 100	48	M	688	8	103	118/80	1.12	110	7	107	4	120/80	120/84	7	448